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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,339	06/18/2007	Robert L. Wolfert	DEX0531US.NP	8696

32800 7590 09/09/2010

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EXAMINER	
HAQ, SHAFIQUL	
ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
09/09/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	10/588,339	WOLFERT ET AL.	
	Examiner	Art Unit	
	SHAFIQUL HAQ	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73,74,76,78,80-82,86-89 and 92-103* is/are pending in the application.

4a) Of the above claim(s) *81 and 88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73,74,76,78,80,82,86-87,89 and 92-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/8/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 73-74, 76, 78, 80-82, 86-89 and 92-103 remain in the case of which claims 81 and 88 are withdrawn from consideration (see the office action of 2/8/2010). Therefore, claims 73-74, 76, 78, 80, 82, 86-87, 89 and 92-103 are examined on merits in this office action.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 73-74, 76, 78, 80, 82, 86-87, 89 and 92-103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 73 recites "measuring free thiols product" in step (c). Step (a) requires reducing active thiols in a sample i.e. producing “reduced thiols” and step (b) requires conversion of the substrate to an “active thiol". However, as described above, step (c) measures “free thiol", which is not recited to be a product in any of the steps (a) or (b). Therefore, it is unclear what is intended by "free thiol" in step (c). Is it "active thiol" or "reduced thiol". The claim should particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 73-74, 76, 78, 80, 82, 86-87, 89 and 92-103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 73 and 86 recites "a compound which reduces active thiol(s)". In the specification the only description for a compound which reduces active thiol(s) is DTNB. There is absolutely no guidance or description of any other compound in the specification for use as "a compound which reduces active thiol" that would be useful for the purpose and process as described in the method steps for detection of Lp-PLA2 in the sample.

During examination, the claims must be interpreted as broadly as their terms reasonably allow. In re American Academy of Science Tech Center, 367 F.3d 1359, 136~), 70 USPQ2d 1827, 1834 (Fed. Cir. 2004). Therefore, the recitation "a compound which reduces active thiols(s)" can be interpreted as encompassing other thiol reducing agents such as DTT and mercaptoethanol. However, there is no written descriptive support and guidance for the use of other reducing agents as described above for "a compound which reduces active thiols" in the specification for the method process as claimed in claim 73. There is no guidance as to whether the reducing agent as described above would be useful in the detection method as claimed in claims 73 and 86. Therefore, the specification fails to provide sufficient

support of the broad use of all reducing agent for the purpose of reducing active thiol(s) in the sample for the purpose of measuring Lp-PLA2 activity with the use of a substrate converted to free thiol product in the presence of enzymatically active Lp-PLA2.

The MPEP states that the purpose of written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject mater later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." See MPEP § 2163. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. In re Glass, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). **Examples and description should be of sufficient scope as to justify the scope of the claims**.

Accordingly, it is deemed that the specification fails to provide adequate written description and clear guidance for all compounds encompassed by "a compound which reduces active thiol(s)" and does not reasonable convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 73, 74, 76, 78, 80, 82 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farooqui *et al* (J. Lipid Res. 1984) in view of Murata *et al* (Chem. Pharm. Biol 1991).

Farooqui *et al* disclose a method for measuring enzymatically activity phospholipases in a sample comprising reaction of the sample with DTNB (i.e. a compound that reduces active thiol), adding a thioester substrate for the phospholipase and measuring formation of free thiol by their reaction with DTNB that produces a detectable thionitrobenzoate from DTNB (page 1557: line 27 of left column to line 33 of right column; Fig. 2 and the paragraph under the heading "DISCUSSION" on page 1560).

Farooqui *et al* do not mention measuring Lipoprotein-associated Phospholipase A2 (also known as Lp-PLA2 or PAF-AH).

Murata *et al* disclose thioester (2-thio-PAF) as substrates for PAF acetylhydrolase (PAF-AH). Murata *et al* teach that PAF acetylhydrolase activity in blood/serum is correlated with respiratory symptoms in asthmatic children. Murata *et al* further disclose that the substrate is useful for measuring PAF acetylhydrolase activity.

Therefore, given the fact that the thioester 2-thio-PAF as taught by Murata *et al* are useful as a substrate for PAF-AH, it would be obvious to one of ordinary skill in the art at the time the invention was made to consider using 2-thio-PAF of Murata *et al* in the method of Farooqui *et al* for spectrophotometric detection of PAF-AH in a sample with the expectation of detection of respiratory symptoms in asthmatic patient with a reasonable expectation of success. Reasonable expectation comes from the teaching of the mechanism of production of active thiol compounds from thioester substrates by phospholipases and detection of the thiol compounds by DTNB (Farooqui et al) and 2-thio-PAF as disclosed by Murata is one of the thioester substrate for PAF-AH.

With regard to claim 74, Murata *et al* teach that PAF acetylhydrolase activity in blood/serum is correlated with respiratory symptoms and thus detection of PAF acetylhydrolase activity in blood/serum would be obvious to one of ordinary skill in the art for diagnosis of asthmatic symptoms.

With regard to claims 76 and 78, Farooqui *et al* teach incubating the sample and reference with DTNB until the slope of the recorder tracing reaches zero but however do not mention the incubation temperature. However, incubation at room temperature or 37C would be obvious for PAF-AH acetylhydrolase as the enzyme is known to show enzymatic activity at these temperatures. Moreover, the adjustment of particular working conditions (such as incubation temperature and duration of incubation) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan and therefore obvious under 35 U.S.C. § 103(a).

With regard to claim 80, as described in the rejection above, combination of the references teach utilizing 2-thio PAF substrate for detection of PAF acetylhydrolase.

With regard to claim 82, Farooqui *et al* teach using reference (page 1557: lines 28-29) and thus comparing free thiol production of the sample to the reference sample would be obvious to one of ordinary skill in the art to avoid non-specific reading.

With regard to claim 92, Murata *et al* teach that PAF acetylhydrolase activity in blood/serum is correlated with respiratory symptoms in asthmatic children and thus monitoring PAF acetylhydrolase activity in a sample from asthmatic children (i.e. patient) would be obvious to one of ordinary skill in the art.

9. Claims 93-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farooqui *et al* (J. Lipid Res. 1984) in view of Murata *et al* (Chem. Pharm. Biol 1991) as described above and further in view of Benitez *et al* (Circulation 2003).

See the above teaching of 2-thio PAF substrate and DTNB for detection of PAF acetylhydrolase. Murata *et al* teach that PAF acetylhydrolase activity in blood/serum is correlated with respiratory symptoms in asthmatic children but failed to teach correlation of PAF-AH activity with coronary artery disease.

Benitez *et al* teach that PAF-AH has been a potential risk factor for coronary artery disease and its plasma concentration and activity are directly correlated with plasma and LDL cholesterol (page 94, see first four lines under the heading "Discussion").

Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to use sample from a patient suspected of having coronary artery disease for detection of PAF-AH activity with the expectation of similarly detection of coronary artery disease and/or establishing a correlation of the enzyme activity with coronary artery disease because Benitez *et al* teach that PAF-AH has been a potential risk factor for coronary artery disease and its plasma concentration and activity are directly correlated with plasma and LDL cholesterol.

With regard to claims 97 and 98, Benitez *et al* teach that PAF-AH inhibition in rabbits slows atherosclerosis progression providing a relationship between PAF-AH and atherogenesis (see introduction) and teach use of specific inhibitor of PAF-AH which is reported to be correlated with reduced atherosclerotic plaque development (see discussion). Therefore, detection of PAF-AH activity in a sample from patient administered with PAF-AH would similarly be obvious to one of ordinary skill in the art for detection of coronary artery disease and/or establishing a correlation of the enzyme activity with coronary artery disease.

10. Claims 86, 87, 89 and 99-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farooqui *et al* (J. Lipid Res. 1984) in view of Murata *et al* (Chem. Pharm. Biol 1991) as described above and further in view of Maret et al (US Patent 5,478,741).

See the above teaching of 2-thio PAF substrate and DTNB for detection of PAF acetylhydrolase.

The above references do not teach putting the assay components in a kit.

Maret et al disclose that components for carrying out immunoassay methods can be packaged in the form of a kit for convenience and such a kit may include an appropriate assay device, antibody reagents, reagents for development of the assay such as buffers and, if needed, reagents for detection of the chosen label (column 6, lines 16-21).

Therefore, since the packaging of components in a kit form is a well-known obvious expedient for ease and convenience in assay performance (Maret et al) and once a method has been established, one skilled in the art would clearly consider compiling in a kit format and change/modify different components of the kit to best suit the assay. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to place the PAF-AH substrates and other necessary components (e.g. DTNB) in the kit for a matter of convenience as taught by the '741 patent.

With regard to claims 99-103, the sample is not a component of the supplied kit and thus the sample "from a patient" has not been given weight for patentability consideration. It is the kit components that are considered for patentability and the kit component includes a compound which reduces active thiols and a substrate that reacts with an enzymatically active Lp-PLA2 to produce a detectable product. Note that the enzymatically active Lp-PLA2 is not a kit component as well. A recitation of the intended use of the claimed invention (e.g. "for measuring enzymatically active Lipoprotein-associated Phospholipase A2" and "from patient") must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Response to Applicant's argument

11. Applicant's arguments and amendments filed 7/8/2010 have been fully considered and are persuasive to overcome the rejections of 2/8/2010 under 35 U.S.C. 112 second but they not persuasive to overcome the rejections under 35 USC 112 first paragraph and 35 USC 103 (a). However, applicant amendments necessitated applying new grounds of rejections under 35 U.S.C. 112 second paragraphs and modifying the rejections under 35 USC 103 to cover claims amendments, which are described in this office action.

With regard to 35 USC 103 rejection over Farooqui *et al*, Applicants argued that in the Farooqui method, free thiol product is not indicative of enzymatically active enzyme in the sample. Instead, the additional step of subtraction of a blank (background DTNB) is required and in contrast, the instant invention provides direct determination of enzymatically active LP-PLA2 in the sample without requirement of subtraction of values from a blank.

The above argument has been fully considered but is not persuasive because the steps involved for measuring (measuring of free thiol) has not been clearly defined in the claim. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). However, in contrast to Applicants' argument, Farooqui *et al* teach the color formed with the thionitrobenzoate product permits the discrimination of spectrophotometric enzyme activity from light scattering by visual inspection of the incubation mixture (page

1560, last four lines on second column), which provides a direct determination of enzymatically active phospholipases.

With regard to 112 first paragraph rejection Applicants argued that as procedures and compounds for reducing active thiol(s) are well known to those skilled in the art, the absence of such specific details in the instant specification cannot be the basis for a lack of written description rejection.

Applicants' argument has been fully considered but is not persuasive because in the specification DNTB is the only compound disclosed in the specification for reducing active thiol(s) for the process claim as recited. There is absolutely no guidance, description and structural characteristic of any other thiol reducing compound in the specification for use as "a compound which reduces active thiol" that would be useful for the purpose and process as described in the method steps for detection of Lp-PLA2 in the sample. As described above in the 35 USC 112, first paragraph rejection, a disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. *In re* Glass, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). Examples and description should be of sufficient scope as to justify the scope of the claims. Markush claims must be provided with support in the disclosure for each member of the Markush group. The court indicated that although applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the

claimed genus and DNTB only is not a representative number of all the molecules falling within the scope of the claimed genus (i.e. reducing agents for active thiols). The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164). In the absence of structural characteristics that are shared by members of the genus; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Conclusion

12. No claims are allowed.

13. Applicants' amendment necessitated new ground(s) of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicant should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported in ipsis verbis, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shafiqul Haq/
Primary Examiner, Art Unit 1641